Challapalli V, Tremont-Lukats IW et al. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Database of Systematic Reviews 2005; Issue 4, CD003345.

Design: Meta-analysis of randomized clinical trials

PICOS:

- **Participants**: patients of any age with neuropathic pain from numerous causes
- **Interventions**: Systemic lidocaine or its oral analogs (mexiletine, tocainide, and flecainide
- **Comparison** intervention: Placebo or any other active drug treatment
- **Outcomes**: Intensity of spontaneous pain or its relief; adverse effects sufficient to cause study withdrawal or reduction in drug dosage
- **Study** types: Randomized double-blind clinical trials with parallel or crossover design

Study search and selection:

- Search databases included Cochrane Central Register of Controlled Trials, MEDLINE (1966-2004), EMBASE (1980-2002) , CancerLit (1963-2002), LILACS (Latin American and Caribbean literature database), SIGLE (System for Information on Grey Literature in Europe) for conference proceedings, and selected authors for additional information on published or unpublished trials
- Quality assessment was done by three authors based on randomization, blinding, and completeness of follow-up
- Search identified 44 trials which were relevant to the review; 14 were excluded for lack of blinding, lack of randomization, being duplicate trials, for being studies of experimental pain; 30 trials were included

Results:

- 11 trials (10 of them crossover trials) of IV lidocaine with 187 patients on lidocaine and 186 on placebo showed superiority of lidocaine to placebo for mean VAS pain scores; the weighted mean difference between lidocaine and placebo was 11.26 points on a scale from 0-100 (95% confidence intervals from 5.22 to 17.30 points); a random effects model was used, and heterogeneity was not apparent (I^2 =24%)
- 9 trials of oral mexiletine (5 crossover, 4 parallel) with 184 mexiletine patients and 193 placebo patients showed superiority of mexiletine to placebo for mean VAS pain scores; the weighted mean difference between mexiletine and placebo was 11.11 points (95% CI, 5.97 to 16.25 points); a random effects model was used, and heterogeneity was not apparent (I^2 =39%)
- For lidocaine and mexiletine combined, with 371 active drug and 379 placebo patients, the weighted mean difference in favor of active drug for pain VAS was 11.18 points (95% CI, 7.40 to 11.18); a random effects model was used, and heterogeneity was not apparent (I^2 =28%)

- For significant pain relief, from 9 lidocaine trials with 115 lidocaine patients and 114 placebo patients, the pooled odds ratio was 5.06 (95% CI, 2.36 to 10.84) in favor of lidocaine
- For significant pain relief, from 5 mexiletine trials with 206 mexiletine and 154 placebo patients, the pooled odds ratio was 2.52 (95% CI, 1.47 to 4.31) in favor of mexiletine
- The 5 trials comparing lidocaine or its oral analogs with other active drugs (carbamazepine, gabapentin, amantadine, or morphine) showed no difference in analgesia
- In placebo-controlled trials, adverse effects were more frequent (35%) with lidocaine or its oral analogs than with placebo (12%); the most common were sleepiness, fatigue, nausea, perioral numbness, metallic taste, and dizziness
- In 5 active drug-controlled trials, the frequency of adverse effects for lidocaine and its oral analogs were similar (31%) and active drugs (31%)
- For active drug-controlled trials, there was heterogeneity of effect for adverse effects (I^2 =65%), but no trial had a statistically significant difference between lidocaine/mexiletine and the comparison drug

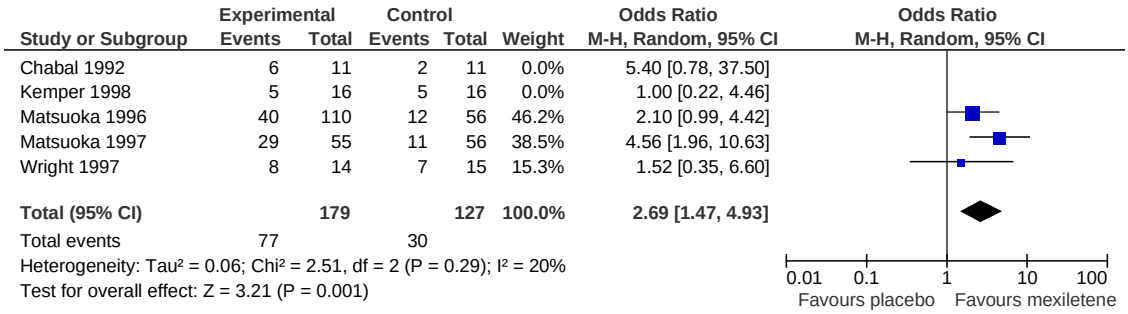
Authors' conclusions:

- Lidocaine and mexiletine were more effective than placebo in decreasing neuropathic pain
- However, the role of systemic local anesthetics for neuropathic pain is difficult to define; more than half of the trials were of low or fair methodological quality in their reporting
- The mean difference of 11 on a scale from 1-100 between lidocaine/mexiletine and placebo is difficult to interpret; due to the bimodal distribution of pain scores, average differences may not capture larger and clinically important differences for some patients
- The responder rates, defined as binary data (success or failure at achieving 33% or 50% relief), agree with the average pain difference results, and also show superiority of local anesthetics to placebo
- Although adverse effects occurred more commonly with local anesthetics than with placebo, the drugs were safe; there were no serious toxicities and few withdrawals due to side effects

Comments:

- Analysis 1.1, the main analysis comparing the efficacy of lidocaine/mexiletine versus control, combines 11 studies, 10 crossover trials and one small parallel trial
- Analysis 1.1 compares pain VAS scores at the end of treatment
- However, when crossover trials are being combined, this is an inefficient use of the data that crossover trials can provide; the most efficient use of crossover data with two periods and two treatments is a paired t-test, based on the changes between baseline and post-treatment pain scores, not on the final pain scores

- Analysis 1.2 is based on response rates, which, while not using paired t-tests, does make use of the individual patient differences between the two treatments, and is likely to be a more efficient use of the crossover data
- Therefore, the discrepancy between Analysis 1.1 (showing a clinically small treatment effect) and Analysis 1.2 (showing a clinically larger treatment effect) may arise from the difference in efficiency of the analyses
- Analysis 1.2, comparing response rates, again appears to analyze crossover trials as if they were parallel trials, when they should be analyzed by the ratio of discordant pairs (the number of patients who responded to the local anesthetic but not placebo divided by the number of patients who responded to placebo but not local anesthetic); patients who responded to both (or neither) contribute nothing to the analysis of a crossover trial
- The authors' judgment of the quality of the studies was based on methods commonly used for parallel group RCTs—randomization, blinding, and withdrawals; however, since the majority of the studies were crossover trials, the quality scoring should have included period and carryover effects and the adequacy of the washout period; these are crucial for the analysis of crossover trials
- Lidocaine and mexiletine were judged to be safe, based on absence of severe toxicity and on few withdrawals
- However, one of the included studies of lidocaine (Attal 2004) reported that 16 of the 22 patients subsequently received mexiletine titrated up to efficacy and side effects, and that 14 of these patients stopped their treatment within less than 3 months due to side effects (n=9) or lack of efficacy (n=5), and that only 2 patients continued to take mexiletine more than 3 months
- The appropriate clinical use of IV lidocaine is not clear; its short duration of action makes it impractical for continued use, and its usefulness to predict the response to mexiletine is also undefined
- Although the reference list states that the authors used published data only for several studies (Wallace 2000b and Wu 2002), the acknowledgments note that data on means and standard errors were obtained from other sources; this illustrates how inexact the data is when it is represented only in the form of bar graphs without tabular displays of the data
- The summary measures in Analyses 1.1 and 1.2 cannot be trusted as estimates of effect size, but qualitative superiority of lidocaine/mexiletine to placebo appear to follow from the data
- Since analyzing crossover trials as if they were parallel group trials is likely to underestimate rather than overestimate the treatment effect, the study is adequate in spite of these errors
- Removing two crossover trials from Analysis 1.2 on mexiletine (Chabal 1992 and Kemper 1998) and including only the parallel group trials does not materially affect the odds ratio (2.69 instead of 2.52):



Assessment: Adequate for a qualitative evidence statement that lidocaine and mexiletine are more effective than placebo for neuropathic pain, but the effect size is very uncertain (results are combined in a way that appears not to suit the design of the included trials, and the quality assessment also omits mention of features which are critical to the analysis of crossover trials)